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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,066	09/20/2001	Hazire Oya Alpar	41577/263691	4735
23370	7590	01/28/2011	EXAMINER	
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ART UNIT	PAPER NUMBER			
		1645		
NOTIFICATION DATE	DELIVERY MODE			
01/28/2011	ELECTRONIC			

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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Office Action Summary	Application No. 09/937,066	Applicant(s) ALPAR ET AL.
	Examiner JaNa Hines	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 29 November 2010.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 56,58-61,63 and 68-73 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 56,58-61,63 and 68-73 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____
- 5) Notice of Informal Patent Application
- 6) Other: _____

DETAILED ACTION

Amendment Entry

1. The amendments filed November 11, 2010 and November 29, 2010 have been entered. Claims 1-55, 62, 64-65 and 67 are cancelled. Claims 56, 58-61, 63, 66 and 72-73 have been amended. Claims 56 and 58-61, 63, 66 and 68-73 are under consideration in this Office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on November 11, 2010 and September 9, 2010 were filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

- a) The objection of claims 63 and 66;
- b) The rejection of claims 52, 66 and 68-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eyles (1998. Vaccine. Vol.16(7):698-707) and Amsden et al., (WO 99/57176); and
- c) The rejection of claims 52, 66 and 68-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (WO 97/20576) in view of Amsden et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 56, 58-61 and 72-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eyles (1998. Vaccine. Vol.16(7):698-707) and Amsden et al., (WO 99/57176).

The claims are drawn to a pharmaceutical composition comprising a biologically active agent capable of generating a protective immune response in an animal or a human and an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof, wherein the biologically active agent and the immunostimulant amount of N-carboxymethyl chitosan or the salt thereof are encapsulated in microspheres or microparticles comprising a polymeric material of a molecular weight 94 kDa or more, and wherein the N-carboxymethyl chitosan or the salt thereof is present in the pharmaceutical composition in an amount of from 0.1 to 10% w/w.

Eyles et al., teach intra-nasal administration of poly-lactic acid microspheres co-encapsulated with *Yersinia pestis* subunits that confer protection from pneumonic plague in mice. *Yersinia pestis* has a capsule that surrounds the bacterium and contains a protein-polysaccharide complex, which was termed the F1 subunit (page 698). Eyles et al., teach that the F1 antigen confers resistance to phagocytosis and both F1 and V

antigens are protective, although there is an additive effect in the combination (page 698, col.2). Eyles et al., teach a pharmaceutical composition comprising poly-(L-lactide) microspheres co-encapsulated with *Yersinia pestis* V and F1 subunits that confer protection from pneumonic plague in mice (page 699, col.2). Eyles et al., teach that the F1 antigen confers resistance to phagocytosis and both F1 and V antigens are protective, although there is an additive effect in the combination (page 698, col.2). It is noted that the F1 peptide subunit is a glycoprotein. The commercially purchased poly-(L-lactide) has a molecular weight of 100 kDa and was used in a modified double emulsion solvent evaporation method (page 699, col.2). The microsphere encapsulated particles had a mean diameter of 5.86um (page 701, col.1). Eyles et al., teach effective vaccination requires affecting or utilizing mucosal surfaces as portals of entry (page 698-699, col.2-1). Furthermore Eyles et al., teach that mucosal vaccination advantageously offers some degree of the induction of systemic immunity in concert with local responses due to translocation of antigenic material (page 699, col.1). Eyles teach that simple mucosal applications are ineffective because of enzymatic or chemical destruction, combined with poor absorption; therefore encapsulation of antigenic material within microparticulate polymeric carriers such as poly-DL-lactide protect the vaccines from degradation and enhance mucosal and systemic absorption (page 699, col.1). Eyles et al., teach that mucosal vaccination advantageously offers some degree of the induction of systemic immunity in concert with local responses due to translocation of antigenic material (page 699, col.1). However Eyles et al., do not teach pharmaceutical compositions comprising N-carboxymethyl chitosan.

Amsden et al., teach the application of microspheres composed of biodegradable, biocompatible polymer and contains a bioactive agent dispersed therein (page 23, lines 3-6). Amsden et al., teach delivering a bioactive agent to a subject in need of treatment (page 23, lines 15-16). Examples of suitable bioactive agents include anti-proliferative agents, steroids, analgesics, narcotic antagonists, antibiotics, anti-fungals, anti-histamines, anti-asthmatics, B-blockers and anti-cancer agents (page 23, lines 18-23). Amsden et al., teach therapeutic microspheres comprising a bioactive agent being a pharmacologically active peptide, antigen, or antibody exemplified by a microsphere that bears an infectious agent antigen for vaccination (page 24, lines 1-3). Microspheres which comprise bioactive agents are incorporated within the microsphere and /or be bound to the surface (page 24, lines 3-5). Amsden et al., teach the composition formed into microspheres composed of hydrophilic polymers selected from polysaccharides such as chitosan, N,O-carbamoyl chitosan, O-carboxymethyl chitosan, N-carboxymethyl chitosan, blends, copolymers and combinations of these polymers (page 9, lines 12-26). Amsden et al., teach the first composition being poly(lactide) and a second composition being co-glycolide or poly(glycolide) at a ratio of 85:15 , see Example 1 at page 26. Amsden et al., teach microspheres incorporated into a second polymer, which are uniformly sized microspheres dispersed throughout a gel or viscous solution or dispersed throughout a solid biodegradable polymer scaffold (page 24, lines 7-10). Amsden et al., teach that polycationic carbohydrates capable of forming particles include chitin derivatives, chitosans, cationic polypeptides, polyamino acids; which are all disclosed by Amsden et al. Amsden et al., teach polymers formed

into microspheres composed of poly(lactide-co-glycolide) (PGLA) and other lipophilic polymers such as polyesters including but not limited to poly-(L-lactide), poly(lactide) as well as protein or polypeptide such as poly(amino acids). It is noted that is a polymeric material has a molecular weight of 100 kDa or more. Amsden et al., teach in the Examples using 10%w/v, 1% w/v, 5%w/v as a polymer within the microsphere. See examples 1-4, pages 24-28.

Therefore, it would have been *prima facie* obvious at the time of applicants' invention to have used the known N-carboxymethyl chitosan as taught by Amsden et al., and modify the compositions to include the biologically active agents and agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by Eyles in order to enhance the mucoadhesive properties for the composition that enhances mucosal adsorption, provides enhanced immunostimulant activity and confers protection from pneumonic plague. One of ordinary skill in the art would have a reasonable expectation of success by modifying the pharmaceutical compositions as taught by Eyles including the combination of the V and F1 antigen of *Yersinia pestis* in the form of microspheres or microparticles as taught by Eyles et al., because Eyles et al., in order to protect labile vaccines from degradation while enhancing adsorption within the N-carboxymethyl chitosan microspheres of Amsden because they are composed of biodegradable, biocompatible polymer while containing a bioactive agent dispersed therein. Thus one of ordinary skill in the art would have a reasonable expectation of success and no more than routine skill would have been required to modify the composition of Eyles to incorporate the N-

carboxymethyl-chitosan of Amsden et al., into the pharmaceutical composition which already comprises a mucoadhesive combined with biological active antigens in microparticle formation to achieve enhanced mucosal absorption.

Response to Arguments

5. Applicant's arguments have been fully considered but they are not persuasive.

The response to arguments regarding Eyles and Amsden are discussed below.

Applicants assert that the Office does not explain why one of ordinary skill in the art would have expected that the modification of the antigen-containing microspheres prepared of a biodegradable, biocompatible polymer, poly-(L-lactide) with another biodegradable, biocompatible polymer, N-carboxymethyl chitosan, would result in any further improvement the mucoadhesive or other properties of the microspheres.

Amsden et al., teach microsphere advantageously provide for large surface areas, easily administered and do not require removal after completion of drug release.

Amsden et al., teach microsphere having uniform size and diameter which can be dispersed in fluid medium, neat form or freeze dried. The microspheres are known to contain a bioactive agent in addition to a polymer. Amsden et al., teach the need and desire for uniformly sized spheres wherein those changes in production create easily controlled microspheres, scaleable to large production and allows the use of variety of reagents. Amsden et al., teach its microspheres are well suited to deliver the drug through the blood stream and demonstrate controlled release abilities. The microspheres of Amsden et al., can be delivered via transdermal, oral, nasal,

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pulmonary, ocular, or parenteral routes, and are useable for both human or non-human animals. The microspheres of Amsden et al., can comprise bioactive agents incorporated within the microsphere and bound to the surface. For example antibodies or fragments can be bound to a microsphere to target delivery of another bioactive agent contained within the microsphere. And the microspheres of Amsden et al., can be produced to be an infectious agent antigen for vaccination.

Therefore contrary to Applicants assertion, Amsden et al., teach why one of ordinary skill would have expected an improvement of the properties of the microspheres.

Applicants urge that the claimed composition possess an unexpected advantage when compared to the combined disclosures of Eyles and Amsden et al.

In particular, Applicants point to the unexpected adjuvant property of N-carboxymethyl chitosan. The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978) (Claims 1 and 6, directed to a method of effecting nonaddictive analgesia (pain reduction) in animals, were found to be anticipated by the applied prior art which disclosed the same compounds for effecting analgesia but which was silent as to addiction. The court upheld the rejection and stated that the applicants had merely found a new property of the compound and such a

discovery did not constitute a new use. While the references do not show a specific recognition of that result, its discovery by appellants is tantamount only to finding a property in the old composition." 363 F.2d at 934, 150 USPQ at 628 (emphasis in original.). In this case, the additional uses of an old composition such as N-carboxymethyl chitosan, is not found patentable.

Furthermore, where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best* 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Claims were directed to a titanium alloy containing 0.2-0.4% Mo and 0.6-0.9% Ni having corrosion resistance. A Russian article disclosed a titanium alloy containing 0.25% Mo and 0.75% Ni but was silent as to corrosion resistance. The Federal Circuit held that the claim was anticipated because the percentages of Mo and Ni were squarely within the claimed ranges. The court went on to say that it was immaterial what properties the alloys had or who discovered the properties because the composition is the same and thus must

necessarily exhibit the properties.). In this case, the Declaration of Peter James Watts under 1.132 shows that trimethyl chitosan and chitosan are different compounds, however the Declaration does not overcome the teaching N-carboxymethyl chitosan of Amsden et al.,, which is the same as that instantly claimed.

Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a *prima facie* case of unpatentability of Spada's polymer latexes for lack of novelty."). Therefore Applicants argument is not found persasussive.

Applicants argue that impermissible hindsight was used when proposing the claimed compositions based on the combination of Eyles and Amsden. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only

from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this, applicant has not pointed to any knowledge which was not within the level of ordinary skill at the time of the invention. Eyles and Amsden teach pharmaceutical composition comprising a biologically active agent capable of generating a protective immune responses and N-carboxymethyl chitosan in an amount of from 0.1 to 10% w/w, which are encapsulated in microspheres or microparticles comprising a poly-(L-lactide), a polymeric material of a molecular weight 94 kDa or more. Pharmaceutical composition and microspheres containing N-carboxymethyl chitosan were already well known in the art.

It is noted that *prima facie* obviousness is not rebutted by merely recognizing additional advantages or latent properties present in the prior art. See *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). It is the position of the Office that the recitation of an additional advantage associated with doing what the prior art suggests does not lend patentability to an otherwise unpatentable invention.

Applicants urge that the combination of Eyles and Amsden et al., fails to disclose or suggest the combination of elements recites by the instant claims. Applicant is reminded that the claims are drawn to a compositions, and the prior art clearly teaches the components of the compositions.

Applicants request Amsden support of teach vaccines that affect or utilize mucosal surfaces; however the claims are not drawn to any utilizing mucosal surfaces. Eyles et al., teach effective vaccination requires affecting or utilizing musocal surfaces

as portals of entry (page 698-699, col.2-1). Eyles et al., teach that mucosal vaccination advantageously offers some degree of the induction of systemic immunity in concert with local responses due to translocation of antigenic material (page 699, col.1). The microspheres of Amsden et al., can be delivered via oral, nasal, or pulmonary routes, and are useable for both human or non-human animals (see page 24, lines 11-13). It is noted that oral administration includes buccal administration, and nasal includes intranasal administration. Therefore Amsden et al., discloses administrations routes that achieve mucosal vaccination.

Applicants urge that the immunostimulating amount of N-carboxymethyl chitosan or the salt thereof is present in the pharmaceutical composition in an amount of from 0.1 to 10% w/w is not disclosed. Furthermore, Amsden et al., teach the composition formed into microspheres composed of N,O- carbomethyl chitosan, N-carboxymethyl chitosan, and combinations of polymers. Amsden et al., teach that polycationic carbohydrates capable of forming particles from 99:1 to 9:1 w/w include chitin derivatives, chitosans, cationic polypeptides, polyamino acids; which are all disclosed by Amsden et al. No more than routine skill is involved in adjusting the amount of a component of a well known composition to suit a particular starting material in order to achieve the results taught in the prior art.

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or

workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (*Claimed process which was performed at a temperature between 40 °C and 80 °C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100 °C and an acid concentration of 10%.*); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (*Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.*). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Finally, when the prior art teaches a range that overlaps or touches the claimed range, then the prior art range discloses the claimed range sufficiently. See MPEP 2144.05 and 2131.02.

Thus, contrary to Applicants assertions the arguments were not found persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 56, 58-59, 61 and 72-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (WO 97/20576) in view of Amsden et al.

The claims are drawn to a pharmaceutical composition comprising a biologically active agent capable of generating a protective immune response in an animal or a human and an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof, wherein the biologically active agent and the immunostimulant amount of N-carboxymethyl chitosan or the salt thereof are encapsulated in microspheres or microparticles comprising a polymeric material of a molecular weight 94 kDa or more, and wherein the N-carboxymethyl chitosan or the salt thereof is present in the pharmaceutical composition in an amount of from 0.1 to 10% w/w.

Illum teaches vaccine compositions for intranasal administration wherein the compositions comprise one or more antigens and chitosan (abstract). The invention further relates to methods of enhancing the immunogenicity of intranasally administered antigens and the use of antigens in combination with an adjuvant for the manufacture of a vaccine composition for intranasal administration to immunize a mammal against a specific disease (page 1, lines 1-6). Chitosans are derivatives of

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chitin or poly-N-acetyl-D-glucosamine wherein the greater proportion of the N-acetyl groups have been removed (page 2, lines 25-28). It is noted that the instant specification exemplifies water-soluble alkylated chitosan derivative or salt thereof polycationic carbohydrates as chitosans or chitin and use chitosan glutamate salt. Illum teaches chitosans are known to be mucosal absorption enhancers and upon intranasal co-administration, chitosan enhances the immune response of antigens and provide an enhanced effect upon the host (page 3, lines 1-6). The preferred concentrations of the chitosan in the compositions are in the range of 0.02 to 10% (page 3, lines 21-240). Illum teaches administration of an antigen together with a particular chitosan derivative in an intranasal composition it is possible to achieve an immune response, i.e., system and local responses to enhances both a protective IgA mucosal immune response and an IgG systemic immune response (page 3-4, lines 25-3). Illum teaches the chitosan is water-soluble and may be produced by deacetylation methods (page 5, lines 20-24). Illum teaches a method of enhancing a protective and systemic response by administering intranasally to a mammal a composition comprising an antigen and an effective amount of a chitosan (page 4, lines 5-9). Particular chitosans such as chitosan glutamate was commercially purchased (page 5, lines 25-28).

Illum teaches the compositions are formulated in the form of microspheres (page 6, lines 23-24). Illum also teaches that the compositions are typically administered parenterally (page 1, lines 20-21). Illum teach the antigens to include proteins from pathogens, recombinant proteins, peptides, polysaccharides, glycoproteins, lipopolysaccharides and DNA molecules (page 4, lines 19-21). Suitable antigens include

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tetanus antigens, such as the tetanus toxoid and diphtheria antigens, such as the diphtheria toxoid (pages 4-5, lines 23-1). Illum teaches the administration of intranasal compositions (page 6 lines 22-24). Example 1 teaches the preparation of an influenzae surface antigen and 1% chitosan glutamate composition. Example 1 teaches that the mice received intranasal or subcutaneous administration. The tables and figures show the levels of protection for the mice. However Illum does not teach pharmaceutical compositions comprising N-carboxymethyl chitosan.

Amsden has been discussed above as teach the application of microspheres composed of biodegradable, biocompatible polymer containing a bioactive agent and N-carboxymethyl chitosan (page 23, lines 3-6).

Therefore, it would have been *prima facie* obvious at the time of applicants' invention to have used the known N-carboxymethyl chitosan as taught by Amsden et al., and modify the compositions to include the biologically active agents and agents capable of generating a protective immune response and providing the compositions in a microparticle formulation as taught by Illum in order to enhance the mucoadhesive properties for the composition that enhances mucosal adsorption, provides enhanced immunostimulant activity and confers protection from pneumonic plague. One of ordinary skill in the art would have a reasonable expectation of success by modifying the pharmaceutical compositions as taught by Illum while enhancing adsorption within the N-carboxymethyl chitosan microspheres of Amsden because they are composed of biodegradable, biocompatible polymer while containing a bioactive agent dispersed therein. Thus one of ordinary skill in the art would have a reasonable expectation of

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success and no more than routine skill would have been required to modify the composition of Illum to incorporate the N-carboxymethyl-chitosan of Amsden et al., into the pharmaceutical composition which already comprises a mucoadhesive combined with biological active antigens in microparticle formation to achieve enhanced mucosal absorption.

Response to Arguments

7. Applicant's arguments filed November 11, 2010 have been fully considered but they are not persuasive.

The rejection of claims 56, 58-59, 61 and 72-73 under 35 U.S.C. 103(a) as being unpatentable over Illum (WO 97/20576) in view of Amsden et al., is maintained for reasons of record.

Again, Applicants assert that the Office action does not explain why one of ordinary skill in the art would have motivated to use N-carboxymethyl chitosan, when disclosure of its advantageous properties is absent from the prior art. Contrary to Applicants statements, Amsden et al., teach their microspheres advantageously provide for large surface areas, are easily administered and do not require removal after completion of drug release. The microspheres of Amsden et al., are produced in uniform size and diameter and can be dispersed in a variety of forms. Amsden et al., teach the need and desire for uniformly sized spheres scaleable to large production and allows the use of variety of reagents. The microspheres of Amsden et al., are well suited to

deliver the drug and demonstrate controlled release abilities. The microspheres of Amsden et al., can be delivered via transdermal, oral, nasal, pulmonary, ocular, or parenteral routes, and are useable for both human or non-human animals. The microspheres of Amsden et al., comprise bioactive agents, including infectious antigens, incorporated within the microsphere and/or bound to the surface for vaccination.

Therefore contrary to Applicants assertion, Amsden et al., teach why one of ordinary skill would have been motivated to incorporate the composition of Amsden et al.

Applicants argue that impermissible hindsight was used when proposing the claimed compositions based on the combination of Illum and Amsden. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, applicant has not pointed to any knowledge which was not within the level of ordinary skill at the time of the invention. Illum and Amsden teach pharmaceutical composition comprising a biologically active agent capable of generating a protective immune responses and N-carboxymethyl chitosan in an amount of from 0.1 to 10% w/w, which are encapsulated

in microspheres or microparticles comprising a poly-(L-lactide), a polymeric material of a molecular weight 94 kDa or more. Pharmaceutical composition and microspheres containing N-carboxymethyl chitosan were already well known in the art.

It is noted that prima facie obviousness is not rebutted by merely recognizing additional advantages or latent properties present in the prior art. See *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). It is the position of the Office that the recitation of an additional advantage associated with doing what the prior art suggests does not lend patentability to an otherwise unpatentable invention.

As previously identified, Applicants urge that the claimed composition possess an unexpected advantage of possessing immunostimulating properties.

However, the discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. *In re Hack*. However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. In this case, the additional uses of an old composition such as N-carboxymethyl chitosan, is not found patentable.

Furthermore, where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). Therefore, the prima facie case can be rebutted by evidence

showing that the prior art products do not necessarily possess the characteristics of the claimed product. Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present.

Therefore Applicants argument is not found persuasive and the rejections are maintained.

Claim Rejections - 35 USC § 103

8. Claims 63, 66 and 68-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amsden and Eyles further in view of Cleary et al., (WO 96/21432 published July 18, 1996).

Both Amsden and Eyles have been discussed above as teaching a pharmaceutical composition comprising having N-carboxymethyl chitosan or a salt thereof and a biologically active agent capable of generating a protective immune response in an animal or a human wherein the microspheres comprise bioactive agents, bound to the surface for vaccination.

Cleary et al., teach sustained and controlled local and systemic release of active agents to adhere to mucosal surfaces (page 3, lines 9-12). Cleary et al., teach modes of delivery to the lungs, by inhalation, along with delivery to the upper or lower respiratory tracts by oral or nasal inhalation and to the nasal mucosa (page 1, lines 20-2 and page 2, lines 13-15). Cleary et al., teach the active agents have therapeutic effects either locally, upon the mucosal tissues and underlying tissues or systemically delivered

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(page 3-4, lines 26-2). Cleary et al., teach mucoadhesive particles having a polymer which is the mucoadhesive itself in particulate form (page 4-5, lines 26-1). Clearly et al., teach the particles as being microspheres, microparticles or microcapsules (page 5, lines 5-6). Cleary et al., teach coating the active substance with a bioerodible mucoadhesive polymer layer (page 7, line 1). Cleary et al., teach a particle having a drug containing core and a mucoadhesive coating made of a polymer that dissolves slowing resulting in retention of the active substance on the mucosal surface for an extended period of time (page 7, lines 5-15).

Therefore it would have been *prima facie* obvious at the time of applicants' invention to modify the pharmaceutical composition comprising having N-carboxymethyl chitosan or a salt thereof and a biologically active agent capable of generating a protective immune response in an animal or a human as taught by Amsden and Eyles wherein the modification incorporates the having the N-carboxymethyl chitosan at the surface of the particle as taught by Cleary et al., in order to provide sustained and controlled local and systemic release of active agents to mucosal surfaces. One of ordinary skill in the art would be motivated to modify the method of administration as taught by Amsden and Eyles because both teach the inclusion of a mucoadhesive is well known and that mucosal absorption enhances the immune response of antigens.

Response to Arguments

9. Applicant's arguments filed November 11, 2010 have been fully considered but they are not persuasive.

Applicants assert that it would not have been obvious to one of ordinary skill in the art using the combined disclosure of Amsden, Eyles and Cleary to arrive at polymer microspheres surface-modified with N-carboxymethyl chitosan and having adsorbed thereon a biologically active agent, as recited by Claim 63.

It is the position of the office action the microspheres of Amsden et al., can comprise bioactive agents bound to the surface wherein bioactive agents such as antibodies or fragments can be bound to the surface microsphere. While Cleary et al., teach coating the active substance with a bioerodible mucoadhesive polymer layer.

In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combinations would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

With respect to applicants have not pointed to what aspects of the composition act in an unpredictable manner. All of the components were known in the prior art.

prima facie obviousness is not rebutted by merely recognizing additional advantages or latent properties present in the prior art. See *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). It is the position of the Office that the recitation of an additional advantage associated with doing what the prior art suggests does not lend patentability to an otherwise unpatentable invention. Therefore, applicants' arguments are not found persuasive and the rejection is maintained.

Oath/Declaration

10. The declaration of peter James Watts under 37 CFR 1.132 filed November 29, 2010 is insufficient to overcome the rejection of claims 56, 58-61, 63, 68-73 based upon insufficiency of disclosure under as set forth in the Office action because: the Declaration does not teach that a pharmaceutical composition comprising a biologically active agent and an immunostimulant amount of N-carboxymethyl chitosan or a salt thereof, are encapsulated in microspheres or microparticles comprising a polymeric material of a molecular weight 94 kDa or more. The declaration does not address is unexpected presence of N-carboxymethyl chitosan within microspheres. The declaration has not detailed what aspects of the composition act in an unpredictable manner. At best, the declaration explains the differences between the properties chitosan and trimethyl chitosan. However, none of the claims are drawn to trimethyl chitosan.

Conclusion

11. No claims allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor Patricia Duffy, can be reached on 571-272-0855. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645